REMARKS

Status of the Claims

Claims 5, 13, 19, and 42 have been amended to recite the limitation that the composition is "free of glycerol and polyethylene glycol polymers." Claims 29, 34, 41, and 49 have been amended to increase the recited percent amino acid sequence identity of the interferon-beta (IFN-β) recited in the claimed compositions from at least 80% to at least 95% and to include the limitation that the claimed IFN-β retains the ability to bind to IFN-β receptors. Support for these amendments may be found throughout the specification, for example, on page 8, lines 16-19, on page 10, lines 1-2, and on page 15, lines 22-28, wherein stabilizers such as glycerol are listed as optional components of the claimed compositions. No new matter has been added by amendment. Claims 5-9, 13-17, 19, 20, 26-43, and 45-49 are pending in the present application. Reexamination and reconsideration of the claims are respectfully requested.

The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

The Examiner has maintained the rejection of claims 5-9, 13-17, 19, 20, 26-43, and 45-49 under 35 U.S.C. § 103 as being obvious over Dorin *et al.* (U.S. Patent No. 5,814,485) in view of Hershenson *et al.* (U.S. Patent No. 5,004,605) and further in view of *The Merck Index* (1989). This rejection is respectfully traversed.

Applicants have discovered pharmaceutical formulations including monomeric IFN-β in an aspartic acid and sodium succinate buffer at a pH of about 3.0 to about 5.0. Applicants have previously made of record, and the Examiner has acknowledged, that Dorin *et al.* fail to teach either the claimed pH range, or aspartic acid or sodium succinate (Office Action, dated November 8, 2004, page 3, lines 4-6). The Examiner contends, however, that "while it is true that Dorin *et al.* (U.S. Patent No. 5,814,485) disclose that the pH of the formulation is adjusted to between 6.0 and 7.5, there is no disclosure that would teach away from the present invention. Further Dorin *et al.* teach that the pH will be chosen not only to optimize the longevity of the IFN-β polypeptide but also to ease administration of the IFN-β polypeptide to humans (see

column 13, lines 48-50), thus providing the motivation to adjust the pH for optimal storage and/or administration" (Office Action, dated April 13, 2006, page 3, lines 8-14).

Applicants submit that, contrary to the Examiner's assertion, the cited passage from Dorin *et al.*, when taken in context, does **not** provide motivation to adjust the pH of a formulation of IFN-β to about 3.0 to about 5.0. In fact, there is no suggestion to formulate the claimed IFN-β compositions within a low pH range; to the contrary, this cited passage specifically teaches away from a pH range of about 3.0 to about 5.0, noting:

> Maintenance of pH is **critical** to prevent such physical and chemical alterations, such as oxidation, during storage of the IFN-β polypeptide. The pH will be chosen not only to optimize the longevity of the IFN-β polypeptide but to ease administration of the IFN-β polypeptide to humans. Usually, the pH of the formulation is adjusted to between 6.0 and 7.5 with NaOH if a sodium containing buffering reagent is used. More preferably the pH is adjusted to 6.5.

See, Dorin *et al.*, col. 13, lines 46-54 (emphasis added). Upon understanding the teachings of Dorin *et al.* that during storage of an IFN-β polypeptide, maintenance of pH is "critical," and that the pH of the formulation is most preferably "adjusted to 6.5," one of skill in the art (who would understand that each pH unit represents a tenfold difference in hydrogen ion concentration) would not be motivated to adjust the pH of a formulation of IFN-β to about 3.0 to about 5.0, which is fifty to five thousand times more acidic than the preferred pH of 6.5 taught by Dorin *et al.*

The Examiner also relies on the Hershenson *et al.* patent to provide the guidance that IFN-β compositions can be formulated at a low pH overlapping the presently claimed pH range. Applicants submit that the combined teachings of these two patents do not render the presently claimed compositions obvious. The Hershenson *et al.* patent teaches "a therapeutically effective amount of a recombinant interferon-β protein dissolved in an inert carrier medium comprising as a stabilizer/solubilizer an effective amount either of glycerol or of polyethylene glycol polymers having an average molecular weight from about 190 to about 1600 daltons." See, for example, column 4, lines 42-48 of the Hershenson *et al.* patent. Hershenson *et al.* explain that "[t]he pharmaceutical compositions of this invention provide a means of maintaining recombinant IFN-β in soluble form and thereby stabilizing it by use of one or more solubilizer/stabilizers of this

invention." Column 6, lines 65-68. The Hershenson *et al.* patent thus teaches compositions that require the use of one or more solubilizers/stabilizers to maintain a solubilized interferon formulation.

In contrast, Applicants' method of formulating IFN-β yields compositions that are free of glycerol and polyethylene glycol polymers. The Hershenson *et al.* patent provides no guidance whatsoever, alone or in combination with the Dorin *et al.* patent, that would lead one of skill in the art to formulate IFN-β in the manner set forth in the presently claimed invention. Rather, it teaches away from Applicants' claimed invention.

The Examiner further alleges that "in the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists" (Office Action, page 3, lines 19-20; citing *MPEP* § 2144.05). However, as discussed above, the Hershenson *et al.* patent provides no guidance whatsoever, alone or in combination with the Dorin *et al.* patent, that would lead one of skill in the art to formulate IFN-β in the manner set forth in the presently claimed invention (*i.e.*, free of glycerol and polyethylene glycol polymers and at a pH of about 3.0 to about 5.0). Rather, it teaches away from Applicants' claimed invention, by disclosing compositions that require the use of one or more solubilizers/stabilizers to maintain a solubilized interferon formulation. As further stated in Section 2144.05 of the *MPEP*, "[a] *prima facie* case of obviousness [based on overlapping ranges] may also be rebutted by showing that the art, **in any material respect**, teaches away from the claimed invention" (emphasis added). In the instant case, Applicants submit that the Hershenson *et al.* patent teaches away from the presently claimed invention in a material respect, as discussed above.

The Examiner also characterizes the Applicants' description of the combination of Dorin *et al.* with Hershenson *et al.*, with regard to teaching the use of glycine in IFN-β compositions, as being inaccurate. Applicants respectfully disagree with this assertion. However, as previously made of record, Applicants have amended the claims to delete glycine (see Response mailed September 27, 2005, page 10, lines 7-8).

The Examiner continues to rely on *The Merck Index* as teaching aspartic acid as a weak acid with a pKa that would be recognized by one of skill in the art as being useful in the presently claimed pH range. "Thus it would be obvious to one of ordinary skill in the art to

substitute aspartic acid for the glycine of Dorin *et al.*, because the artisan of ordinary skill would recognize, based on the teachings of the Merck Index, that it would be equally effective for buffering at this pH" (Office Action, page 5, lines 6-9).

Applicants respectfully disagree with this assertion, and submit that there is no suggestion or motivation to combine the teachings of *The Merck Index* concerning pKa data for aspartic acid with either Dorin *et al.* and/or Hershenson *et al.* As previously made of record, Applicants submit that the reference to aspartic acid, within the context of a description of its physico-chemical properties in *The Merck Index*, merely invites experimentation (see Response mailed September 27, 2005, page 10, lines 9-14); yet an invitation to experiment is not sufficient grounds to reject an invitation as obvious. Where the prior art gives only general guidance as to the particular form of the invention or how to achieve it, as here, obviousness may not be found. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 90-91 (Fed. Cir. 1986).

The Examiner asserts that the teachings of *The Merck Index* regarding the physico-chemical properties of aspartic acid are not an invitation to experiment, because the Dorin *et al.* and Hershenson *et al.* patents "clearly provide motivation to modify the composition" (Office Action, page 5, line 10). However, as discussed above, one of ordinary skill in the art would not be motivated to formulate IFN-β free of glycerol and polyethylene glycol polymers (contra Hershenson *et al.*), and at a pH of about 3.0 to about 5.0 (contra Dorin *et al.*). Hence, Applicants continue to submit that the reference to aspartic acid, within the context of a description of its physico-chemical properties in *The Merck Index*, merely invites experimentation. Finally, even if the teachings of *The Merck Index* are combined with the teachings of the Dorin *et al.* and Hershenson *et al.* patents, the combined teachings still fail to provide the guidance to formulate IFN-β in the absence of the solubilizer/stabilizers taught as critical components of the Hershenson *et al.* compositions.

The Examiner also asserts that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references" (Office Action, page 5, lines 10-12). Applicants submit that they have not attacked the references individually, but have presented cogent arguments as to why Dorin *et al.*, Hershenson *et al.* and *The Merck Index*

cannot be combined to arrive at the claimed invention.

Finally, the Examiner contends that Applicants' assertion that the instant formulations of IFN-β are free of glycerol and polyethylene glycol polymers is not found persuasive because the instant claims recite the transitional phrase "consisting essentially of." Applicants respectfully disagree with the Examiner for the reasons already made of record. However, solely to advance prosecution, and to make it clear that the claims do not read on compositions comprising glycerol and polyethylene glycol polymers, independent claims 5, 13, 19, and 42 have been amended to recite the limitation that the claimed compositions are "free of glycerol and polyethylene glycol polymers."

In view of the amendments and arguments presented above, Applicants contend that a *prima facie* case of obviousness under 35 U.S.C. §103 has not been established. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph, Written Description, Should Be Withdrawn

Claims 29, 34, 41, and 49 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement of Section 112. Specifically, the Examiner asserts that "[t]he specification does not provide written description to support the genus encompassed by the instant claims" (Office Action, page 7, lines 1-2). This rejection is respectfully traversed. However, to expedite prosecution of this case, Applicants have amended claims 29, 34, 41, and 49 to recite at least 95% amino acid sequence identity.

The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1, 'Written Description' Requirement" state that a genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties." 66 Fed. Reg. 1106 (January 5, 2001). This is in accordance with the standard for written description set forth in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), where the court held that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or

chemical name' of the claimed subject matter sufficient to distinguish it from other materials." 119 F.3d at 1568, citing *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993).

The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims."). In the instant case, the Examiner asserts that the specification "does not disclose all possible variants of IFN-β that has at least 80% amino acid identity to SEQ ID NO:1" (Office Action, page 6, lines 21-22). As noted above, Applicants have amended claims 29, 34, 41, and 49 to recite compositions including an IFN-β having an amino sequence with at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO:1, and submit that the recitation of at least 95% sequence identity is a very predictable structural requirement encompassed by the claimed invention.

A satisfactory disclosure of a "representative number" of species depends on whether one of skill in the art would recognize that the applicants were in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). Applicants submit that the knowledge and level of skill in the art would allow a person of ordinary skill to envision the claimed invention, *i.e.*, a composition including an IFN-β having an amino sequence with at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO:1.

Furthermore, as noted above, the description of a claimed genus can be by structure, formula, chemical name, or physical properties. See also *Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), citing *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). The recitation of a predictable structure of a sequence comprising an amino sequence with at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO:1 is sufficient to satisfy the written description requirement. These structural limitations are sufficient to distinguish the claimed compositions including an IFN-β having an amino sequence with at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO:1.

Applicants have further provided the functional characteristic that distinguishes the claimed compositions of the genus. Specifically, the claims recite that the IFN-β retains the ability to bind to IFN-β receptors; thereby providing a functional characterization of the amino acid sequences claimed in the genus. Accordingly, both the structural properties **and** the functional properties that characterize the claimed genus are specifically recited in the claims. Therefore, Applicants have conveyed with reasonable clarity to one skilled in the art that they were in possession of the claimed invention. Applicants show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In view of the above amendments and remarks, Applicants submit that all grounds for rejection under 35 U.S.C. § 112, first paragraph, written description, have been overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph, Enablement, Should Be Withdrawn

Claims 29, 34, 41, and 49 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement of Section 112. Specifically, the Examiner asserts that "the specification, while enabling for IFN-β polypeptides of SEQ ID NO:1 and 2, does not reasonably provide enablement for all variants IFN-β (80% identity to SEQ ID NO:1)." This rejection is respectfully traversed.

As discussed above, in order to expedite prosecution, Applicants have amended independent claims 29, 34, 41, and 49 to recite compositions including an IFN-β having an amino sequence with at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO:1, wherein the IFN-β retains the ability to bind to IFN-β receptors. In contrast to the conclusion reached by the Examiner, Applicants submit that support is provided for both the sequence identity limitation of the claims and the functional limitation of the claims. Guidance for determining percent identity of sequences is provided in the specification on page 8, line 16,

continuing through page 9, line 30. The procedures for making nucleotide sequences encoding IFN-β variants are conventional in the art (see, *e.g.*, page 10, lines 9-17 of the specification, which lists a number of exemplary references for such procedures). Additionally, methods for assaying IFN-β activity are routine in the art (see, *e.g.*, page 10, lines 1-8 of the specification, which lists a number of exemplary references for such procedures). Thus, support is provided to enable one of skill in the art to make and use compositions including an IFN-β having the functional and structural limitations of the claims.

When rejecting a claim under the enablement requirement of section 112, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP § 2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In this case, the Examiner relies heavily on "lack of guidance" (Office Action, pages 9-11). For example, on page 9, lines 9-11, the Examiner asserts that "[w]hile it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited" (citing: Wells, *Biochemistry* 29:8509-17, 1990; Ngo *et al.*, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-95, 1994). However, Applicants respectfully contend that these isolated references simply stand for two propositions: 1) those of skill in the art are readily able to determine whether a particular amino acid change affects a biological activity of a protein, and 2) mutagenesis studies demonstrate that proteins are highly plastic in tolerating amino acid changes. Consequently, one of skill in the art would be able to determine the functionality of IFN-β encompassed by the claimed compositions without resorting to undue experimentation.

The Federal Circuit has repeatedly stated that enablement is not precluded by the necessity for some experimentation, so long as the experimentation needed to practice the invention is not undue, and that a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance as to how the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the instant case, the quantity of experimentation required to practice the claimed invention amounts to two steps. First, generating a composition including an IFN-β having an

amino sequence with at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO:1. Second, assaying the composition for functional (*i.e.*, IFN-β) activity. As described above, such assays are well known in the art. One of skill in the art would appreciate that both of these steps are within the skill of those in the art and that this degree of experimentation is not considered undue. "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original).

In view of the above amendments and remarks, Applicants submit that all grounds for rejection under 35 U.S.C. § 112, first paragraph, enablement, have been overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §§ 103 and 112 are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned attorney.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Customer No. 45853 **ALSTON & BIRD LLP** Bank of America Plaza 101 South Tryon Street, Suite 4000 Charlotte, NC 28280-4000 Tel Raleigh Office (919) 862-2200 Fax Raleigh Office (919) 862-2260	"Express Mail" mailing label number EV 395779975US Date of Deposit September 13, 2006 I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 Nora C. Martinez